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Attorney Docket No. 019496-006700US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of:

Yen Choo et al.

Application No.: 09/646,353

Filed: November 27, 2000

For: NUCLEIC ACID BINDING PROTEINS

Examiner: Teresa D. Wessendorf

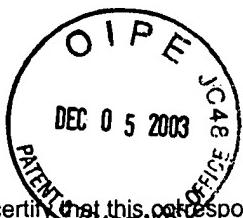
Art Unit: 1639

APPELLANT'S BRIEF UNDER 37 CFR  
§1.192

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By Kristi Cope

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Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

REAL PARTY IN INTEREST:

Gendaq Ltd., a wholly owned subsidiary of Sangamo Biosciences, Inc.

RELATED APPEALS AND INTERFERENCES:

An appeal has been filed in commonly owned copending application 09/424,482.

However, the claims and issues in the respective appeals are not closely related.

STATUS OF CLAIMS:

Claims 1-29 are pending. Claims 1, 2, 5-22, 24 and 27 are withdrawn from consideration. Claims 3, 4, 23, 25, 26, 28 and 29 stand rejected. All rejected claims are appealed. The claims are listed in Appendix A.

STATUS OF AMENDMENTS:

A final office action was mailed July 14, 2003. An amendment after final is filed herewith. The amendment after final amends the specification to correct informalities relating the sequence listing, which were in part noted by the Examiner in the final office action. These amendments have no bearing on the merits of this appeal. The amendment also makes a minor amendment to claim 4 that simplifies an issue raised by the Examiner under 35 USC 112, second paragraph. The listing of claims assumes the amendment after final will be entered although this has not yet been determined.

SUMMARY OF THE INVENTION:

The invention on appeal as defined by claim 3 is directed to methods of binding a zinc finger polypeptide to a triplet of nucleotides that includes a methylated cytosine nucleotide(5-meC). Binding specificity for the 5-meC residue is conferred by placing an alanine residue at position+3 of the alpha helix of the zinc finger that binds to the triplet. The application provides data showing that placing an alanine at this position of a zinc finger causes the zinc finger to specifically bind to a triplet in which the central residue is 5-meC without specifically binding to a triplet in which the central residue is unmethylated cytosine (see, e.g., pp. 36-37). The method comprises two steps. First, a zinc finger polypeptides is prepared by placing an alanine residue at position +3 of the alpha helix of the zinc finger (see, e.g., p. 4, lines 10-15). Then the zinc finger polypeptide is exposed to a target sequence, and the DNA binding polypeptide binds to the target sequence (see e.g., p. 26, lines 15-25). The binding of the zinc finger polypeptide to its target sequence has a number of distinct applications. In some application, the binding is used diagnostically to detect a target sequence (p. 25, lines 19-24). In other applications the binding is used to regulate transcription of the target sequence (p. 26, lines 1-9). In other applications, the zinc finger polypeptide is linked to a restriction enzyme and the binding is used to cleave the target sequence (p. 25, lines 25-31).

ISSUES:

1. Whether the specification provides written description of claims 3, 4, 23, 25-26 and 28-29 as required by 35 USC 112, first paragraph.
2. Whether claims 3-4, 23, 25-26 are indefinite under 35 USC 112, second paragraph.
3. Whether claims 3, 4, 23, 25-26 and 28-29 stand rejected as anticipated by Choo, Comment, XP-002116419 (1998) under 35 USC 102(a).
4. Whether claims 3, 4, 23, 25-26 stand rejected as anticipated by Choo, UK 9805576.7 under 35 USC 102(d).

GROUPING OF THE CLAIMS:

The rejected claims do not stand or fall together. As can be seen from the statement of issues, different rejections have been applied to different claims.

ARGUMENT

Issue 1: The Specification Provides Written Description of Claims 3, 4, 23, 25-26 and 28-29 as Required by 35 USC 112, first paragraph

In the final office action, the Examiner says the specification does not provide written description of a "method for binding a DNA binding polypeptide to a DNA triplet in a target DNA sequence" and "exposing the DNA binding polypeptide to the target DNA" in the context of the claims. The Examiner says that the specification describes a method of determining the presence of a target modified nucleic acid, and does not describe a method for binding a DNA binding polypeptide to its target. The Examiner also says the claimed method does not fall within the statutory subject matter of a method of making or a method of using. The Examiner says the reference to an "exposing" step at p. 26, lines 20-21 is part of a method for determining the presence of a target modified nucleic acid molecule not a method for binding a DNA binding polypeptide to a target DNA (final office action at pp. 3-4).

The rejection raises two separate issues that appellants address in turn. The first is strictly an issue of statutory subject matter under 35 USC 101 notwithstanding it having been raised by the Examiner in the context of 35 USC 112, first and second paragraph. The Examiner

is apparently taking the position that statutory subject matter is confined to methods of making and using and does not include the claimed methods of binding. However, the definition of statutory subject matter is not confined to methods of making or using. "Whoever invent or discovers any new and useful process, machine, manufacture or composition of matter, or any new and useful improvement thereof, may obtain a patent....." 35 USC 101. The presently claimed methods are directed to a combined method of making and using. This constitutes a new and useful process, which is all that is required by 35 USC 101.

The second issue raised in the final office action is written description of the claimed methods. The written description requirement does not require *in haec verba* antecedence in the originally filed application. *Staehelin v. Secher*, 24 USPQ2d 1111, 1117 (Fed. Cir. 1991). All that is required is that the description convey with reasonable clarity to a person of skill in the art that the inventor was in possession of whatever is now claimed. *Vas-Cath v. Mahurka*, 19 USPQ2d 1111,1117 (Fed. Cir. 1991). Here, present claims 3 and 4 differ from claims 3 and 4 as filed in containing an additional step of "exposing the DNA binding polypeptide to a target DNA sequence, whereby the DNA binding polypeptide binds to the target DNA sequence" and a corresponding amendment of the preambles. However, it is submitted that the specification evidences with reasonable clarity that appellants were in possession of this additional step. The specification describes methods of producing zinc finger polypeptides that bind to a target nucleic acid containing a modified nucleic acid base(5-meC in the present claims) (see e.g., p. 5, lines 24-26, original claim 1, the Title and Abstract). The specification also describes several uses of these zinc finger polypeptides. For example, the zinc finger proteins can be used as diagnostic tools for identifying the presence of nucleic acids containing the target sequence (specification at p. 25, lines 20-23), for cleaving a methylated target sequence (p. 35, lines 25-32 and Example 5) or for regulating genes containing the target sequence (p. 26, lines 1-9). In all of these uses it is inherent that the zinc finger polypeptides must be exposed to and bind to their target sequence to achieve the desired result. In diagnostic applications involving detecting a target sequence, the exposing step is explicitly stated in the specification at p. 26, lines 20-22. The exposing step is also illustrated in the Examples (see, e.g., paragraph bridging pp. 36-37). Because all of the disclosed uses of zinc finger polypeptides inherently require exposing the zinc finger polypeptides to a target sequence, such that the zinc

finger polypeptide binds to the target sequence, it would be understood that the explicit recital of an exposing step in the context of the diagnostic method was exemplary only, and that this step also occurs in other uses. Therefore, the specification conveys with reasonable clarity that appellants were in possession of a method of preparing a zinc finger polypeptide and exposing it to a target sequence such that the zinc finger polypeptide binds the target regardless of which of the disclosed uses is ultimately pursued.

For these reasons, it is submitted that claims 3 and 4, and other pending claims dependent therefrom, satisfy 35 USC 112, first paragraph, and the rejection should be reversed.

Issue 2: Claims 3-4, 23, 25-26 are Not Indefinite under 35 USC 112, second paragraph

Claims 3-4, 23, 25-26 stand rejected as indefinite. The Examiner says claims 3 and 4 are confusing in that the body of the claim recites steps of preparing a zinc finger polypeptide and exposing it. The Examiner says the claim does not recite positive method steps, is not a method of making or using as required by statute, and does not recite the steps by which the process of making is accomplished (final office action at p. 5).

Appellants respond that the step of preparing a zinc finger polypeptide is intentionally drafted to be generic to various methods of preparation. Breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 169 USPQ 597 (CCPA 1971). For example zinc finger proteins can be prepared either by linking amino acids together or by producing a nucleic acid encoding the zinc finger protein and then expressing it. The step of preparing a zinc finger polypeptide, although generic to different methods of preparation, is a positive method step, as is the step of exposing a zinc finger polypeptide to a target sequence. Finally, as discussed above, the statute (i.e., 35 USC 101) does not require the preamble to a method claim to recite a method of making or using.

The Examiner rejects claims 4 on the basis that the conditional requirement implied by the term "if" is indefinite (final office action at p. 5). It is noted that it was only in the final office action that the Examiner clarified that the basis for this rejection resided in the word "if." Thus, this is appellants' first opportunity to respond to this basis of rejection.

With respect to element (e) in claim 4, the conditional step is redundant because the claim includes only one possibility for the middle base, namely "5-meC". Therefore, the

conditional phrase has been deleted from element (e) in the accompanying amendment after final.

With respect to the other elements of claim 4 reciting the term "if," appellants maintain that this term is as precise as the subject matter permits. If the claims, read in light of the specification reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the statute demands no more. *Shatterproof Glass Corp. v. Libbey Owens Ford Co.*, 225 USPQ 634 (Fed. Cir. 1985). Here, claim 4 specifies rules for designing a zinc finger polypeptide depending on the composition of a target triplet. In the 5' position of the triplet, there are four possible nucleotides that could occupy the position. These rules are specified as elements (a)-(d). Likewise, there are four possible nucleotides that can occupy the 3' position of the triplet. These are specified in rules (f)-(i). In any particular triplet, only one nucleotide occupies the 5' position and only one nucleotide the 3' position. Accordingly, only one of rules (a)-(d) and one of rules (f)-(i) is used in design of a zinc finger to any triplet. In the circumstances, selection between rules (a)-(d) and (f)-(i) is inherently conditional depending on the composition of the triplet for which a zinc finger is being designed. It is not seen how this conditional selection can be conveyed other than by use of the term "if."

Appellants note that there is no *per se* rule against the term "if" in a claim. See MPEP 2173.02 ("Office policy is not to employ *per se* rules in making technical rejections"). The Examiner has not indicated that she is unable to understand what is being claimed because of the use of the term "if" or suggested any alternatives that can be used. For the reasons, discussed above, it is submitted that this language is as precise as the subject matter permits, and the rejection should be reversed.

The Examiner maintains the rejection to the term "not Asp" for failing to distinctly point out the metes and bounds of the any amino acid besides Asp (final office action at p. 5, last paragraph). Appellants disagree. The primary purpose of § 112, second paragraph, is to apprise the public as to what constitutes infringement. Another purpose of the requirement is to provide a clear measure of the invention in order to facilitate determinations of patentability. *United Carbon Co. v. Binney Co.*, 317 U.S. 228, 236 (1942). Here, for any amino acid one can

determine whether the amino acid is or is not Asp. Such is all that is required to determine relevance of prior art or infringement. 35 USC 112, second paragraph requires no more.

The Examiner maintains that claim 26 is indefinite in not further limiting claim 3 (final office action at p. p. 6). The Examiner says the additional steps of randomization and screening in claim 26 broaden the scope of claim 3 from which claim 26 depends (final office action at p. 6). Appellants disagree. Claim 3 as phrased requires a step of preparing a zinc finger polypeptide, and does not specify one way or the other whether or not additional steps of randomization and screening are performed. Thus, the claim would include methods in which steps of randomization and screening are performed and methods in which they are omitted. Claim 26 by contrast, requires steps of randomization and screening. Thus, claim 26 further limits claim 3.

The Examiner says there appears to be a lack of nexus between method steps of preparing and exposing for binding effect stating that "all polypeptides binds [sic] to DNA one way or another" (final office action, sentence bridging pp. 6-7). The Examiner also says that it is not clear as to the step included in the "whereby" clause of claim 3 (final office action, paragraph bridging pp. 6-7). In response, the two steps in claim 3 are related as method of making and method of using. The first step prepares a zinc finger polypeptide and the second step uses the zinc finger polypeptide to bind its target sequence. The Examiner has not provided an evidentiary source for the statement that all proteins bind DNA, or explained why, even if true, this would render the claims indefinite. The "whereby" clause simply states the result of contacting the zinc finger polypeptide with its target sequence, namely, the zinc finger polypeptide binds to the target sequence.

The Examiner says that claim 26 is indefinite in reciting "screening" in that the base claim recites only a binding between a DNA binding polypeptide and its target. The Examiner says the claim does not clearly state at what stage the screening is performed. The Examiner also says the terms "improve" and "regulates" are relative terms, and that a skilled person would not be able to determine their scope (final office action at p. 7).

Appellants respond that the stage in the method at which randomization and selection is performed is not critical. For example, these steps could logically be performed after a zinc finger binding polypeptide has been prepared but before contacting the zinc finger protein

with its target or could be performed after the zinc finger polypeptide has been contacted with its target. Because the order of steps is not critical, this has not been specified in the claim 26. That the claim does not specify the order of steps is an issue of breadth not indefiniteness. As discussed above, breadth of a claim is not to be equated with indefiniteness.

The meaning of the term "improve" is apparent from the context of claim 26. The claim specifies that steps of randomization and screening improve the binding characteristics of a DNA binding polypeptide. Because the steps of randomization and screening improve the binding characteristics, it is apparent that the improvement is determined by comparing the binding characteristics after performing these steps with those before performing the steps.

Similarly, claim 29 requires that binding of a DNA binding polypeptide regulate transcription of a gene. Because claim 29 covers situations in which the binding of the DNA binding polypeptide causes regulation of transcription, it is apparent from the claim that the regulation is determined by comparing before and after binding the DNA binding polypeptide. Claim 28 is said to be unclear as to the detecting step as to how binding is to be detected (final office action at p. 8). The Examiner also suggests this step be incorporated into the main claim. In response, claim 28 is intended to be generic to any detection format. It is well known that a variety of formats are possible for detecting binding interactions. Such formats can vary in, for example, whether a solid phase is used, which component is linked to the solid phase if present, whether a label is employed and if so, which component is labeled, and whether a secondary labeling agent is used, among other factors. The present claim is intended to include all such formats. As previously discussed, breadth of a claim is not to be equated with indefiniteness.

Appellants also decline to incorporate the step from claim 28 into the base claim. The base claim is intended to be generic to a number of different applications of zinc finger proteins, such as diagnostics, cleaving a target sequence and regulating a target gene. Although all of these applications require exposing a zinc finger polypeptide to a target sequence, whereby the zinc finger polypeptide binds to the target sequence, not all of the applications necessarily require detection of the binding. For example, when a zinc finger polypeptide is used to regulate a target gene, binding can be inferred indirectly from the regulation, but it is not necessary to perform a separate step to detect binding. For these reasons, it is submitted that base claim 3 is

appropriately phrased to be generic to the various disclosed applications of zinc finger polypeptides.

For these reasons, reversal of the rejection is respectfully requested.

Issue 3: Claims 3, 4, 23, 25-26 and 28-29 are Not Anticipated by Choo, Comment, XP-002116419 (1998) under 35 USC 102(a)

Claims 3, 4, 23, 25-26 and 28-29 stand rejected as anticipated by Choo, Comment, XP-002116419 (April 1998) (final office action at p.8). In previous prosecution, Appellants pointed out that Choo was not prior art because it is dated after their priority date of March 31, 1998 (response of March 28, 2003). However, the Examiner disagrees that the priority document of March 31, 1998 provides support for a method of binding as presently claimed. The Examiner also says that cited Choo paper has different authorship than the inventorship of the present application (final office action at p. 8).

The issue of written description for the binding step in claims 3 and 4 in the priority document filed March 31, 1998 is essentially the same as the issue of written description in the present application discussed above under issue one. The March 31, 1998 priority document discloses the same elements supporting written description as does the present application. For example, the priority document discloses methods for producing a zinc finger polypeptide that binds a target sequence (p. 3, lines 19-22 of priority document). The priority document also discloses a variety of applications of zinc finger polypeptides inherently requiring exposing a target sequence to a zinc finger polypeptide, such that the zinc finger polypeptide binds to the target sequence. These applications include diagnostics, cleaving a target sequence, and regulating transcription of a gene as in the present application (p. 23, lines 1-12 of priority document). The priority application also expressly discloses an "exposing" step in the context of determining the presence of a target nucleic acid (p. 23, lines 17-26 of priority document). Because all of the disclosed uses of zinc finger polypeptides in the priority document inherently require exposing a zinc finger polypeptide to a target sequence and binding of the zinc finger polypeptide to the target sequence, it would be understood that the explicit recital of an exposing step in the context of the diagnostic method was exemplary only, and that this step also occurs in other uses. Therefore, the priority document, as the present specification, conveys with reasonable clarity that appellants were in possession of a method of preparing a

zinc finger polypeptide and exposing it to a target sequence such that the zinc finger polypeptide binds the target regardless of which of the disclosed applications of zinc finger polypeptides is ultimately pursued.

Although the entitlement to priority of other claims has not been questioned by the Examiner, appellants briefly note that GB 9806895.0 filed March 31, 1998 provides support for all pending claims. This priority document contains a corresponding claim for each of claims 3, 4, 23 and 25 in the present application (with the exception of the binding step discussed above in claims 3 and 4). The priority document also provides support for present claims 26, 28 and claim 29 at e.g., pp. 10-12; p. 23, line 26; p. 23, lines 6-12 respectively of the priority document.

Therefore, the priority document satisfies 35 USC 112, first paragraph for all of the pending claims. Accordingly, the cited Choo reference, which is dated after the priority document, is not prior art.

The Examiner also raises the issue of the authorship of the cited Choo reference differing from the currently named inventorship of the present application. However, 35 USC 102(a) provides

A person shall be entitled to a patent unless--  
(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent,

The statute thus requires both that the cited publication be by another *and* before the invention thereof of the applicant for patent. In other words, that a publication be by another is necessary but not sufficient for the publication to be prior art under 35 USC 102(a). Here, the cited publication was not before the invention thereof of the present inventive entity because of the entitlement to March 31, 1998 priority date predating that of the cited publication, as discussed above. Thus, irrespective of a difference in authorship and inventorship, the cited publication is not prior art under 35 USC 102(a).

For these reasons, reversal of the rejection is respectfully requested.

Issue 4: Claims 3, 4, 23, 25-26 are Not Anticipated by Choo, UK 9805576.7 under 35 USC 102(d)

Claims 3, 4, 23, 25-26 stand rejected over Choo (UK 9805576.7) (final office action at p. 8). In previous prosecution, Appellants pointed out that the cited application was not filed more than 12 months before the effective US filing date of the present application. The cited application was filed March 17, 1998 and the present application has an effective filing date of March 17, 1999 via PCT/GB99/00816 of which the present application is the US national phase. Appellants also pointed out that the cited application was abandoned and had not issued as a patent. In the final office action, the Examiner says that the cited application does not have to mature as a patent to be prior art under 35 USC 102(d) in that the statute provides in the alternative for maturation into an inventor's certificate. The Examiner also says that the inventive entity is different on the cited application from the present application (final office action at p. 9).

35 USC 102(d) provides:

A person shall be entitled to a patent unless--  
the invention was first patented or caused to be patented, or  
was the subject of an inventor's certificate, by the applicant  
or his legal representatives or assigns in a foreign country  
prior to the date of the application for patent in this country  
on an application for patent or inventor's certificate filed  
more than twelve months before the filing of the  
application in the United States.

Thus, the statute requires that the cited application (1) be filed more than 12 months before the effective date of the application at issue, *and* (2) the cited application mature into a patent or inventor's certificate. Here, the cited application was not filed more than 12 months before the effective date of the present application. To reiterate, the cited application was filed March 17, 1998 and the present application has an effective filing date of March 17, 1999 via PCT/GB99/00816 of which the present application is the US national phase. This fact is alone sufficient to prevent citation of the Choo application under 102(d). In addition, the cited application was abandoned and did not mature into either a patent or an inventor's certificate. This fact, also is alone sufficient to preclude a rejection under 102(d).

35 USC 102(d) also requires that the cited application be by the "applicant or his legal representative or assigns." Insofar as the Examiner is alleging that the inventive entity of

the cited application is different from the present application, the Examiner provides still a third reason that the cited application is not prior art under 35 USC 102(d).

For all of these reasons, it is respectfully submitted that the rejection should be reversed.

CONCLUSION

For the reasons discussed above, it is respectfully submitted that all rejections should be reversed, thereby placing the claims in conditions for allowance.

Please deduct the requisite fee, pursuant to 37 CFR § 1.17(c), of \$160 from deposit account 20-1430 and any additional fees associated with this Brief. The original and three copies of this Brief are being submitted.

Respectfully submitted,



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## APPENDIX A

### LISTING OF CLAIMS

#### APPENDIX A: LISTING OF CLAIMS

Claim 3. A method for binding a DNA binding polypeptide of the Cys2 His2 zinc finger class to a DNA triplet in a target DNA sequence comprising 5-meC as the central residue in the target DNA triplet, the method comprising preparing a DNA binding polypeptide of the Cys2 His2 zinc finger class to bind to the DNA triplet, wherein binding to the 5-meC residue by an  $\alpha$ -helical zinc finger DNA binding motif of the polypeptide is achieved by placing an Ala residue at position +3 of the  $\alpha$ -helix of the zinc finger, and exposing the DNA binding polypeptide to the target DNA sequence, whereby the DNA binding polypeptide binds to the target DNA sequence.

Claim 4. A method for binding a DNA binding polypeptide of the Cys2 His2 zinc finger class to a DNA triplet in target DNA sequence comprising 5-meC, but not to an identical triplet comprising unmethylated C, the method comprising preparing a DNA binding polypeptide of the Cys2 His2 zinc finger class to bind to the triplet comprising 5-meC, wherein binding to each base of the triplet by an  $\alpha$ -helical zinc finger DNA binding motif in the polypeptide is determined as follows:

- a) if the 5' base in the triplet is G, then position +6 in the  $\alpha$ -helix is Arg or position ++2 is Asp, or position +6 in the  $\alpha$ -helix is Arg and position ++2 is Asp;
- b) if the 5' base in the triplet is A, then position +6 in the  $\alpha$ -helix is Gln or Glu and ++2 is not Asp;
- c) if the 5' base in the triplet is T, then position +6 in the  $\alpha$ -helix is Ser or Thr and position ++2 is Asp; or position +6 is a hydrophobic amino acid other than Ala;
- d) if the 5' base in the triplet is C, then position +6 in the  $\alpha$ -helix is any amino acid, provided that position ++2 in the  $\alpha$ -helix is not Asp;
- e) position +3 in the  $\alpha$ -helix is Ala;
- f) if the 3' base in the triplet is G, then position -1 in the  $\alpha$ -helix is Arg;
- g) if the 3' base in the triplet is A, then position -1 in the  $\alpha$ -helix is Gln and position +2 is Ala;
- h) if the 3' base in the triplet is T, then position -1 in the  $\alpha$ -helix is Asn; or position -1 is Gln and position +2 is Ser;

**APPENDIX A**  
**LISTING OF CLAIMS**

i) if the 3' base in the triplet is C, then position -1 in the  $\alpha$ -helix is Asp and Position +1 is Arg; and exposing the DNA binding polypeptide to the target DNA sequence, whereby the DNA binding polypeptide binds to the target DNA sequence.

Claim 23. The method according to claim 3 or 4, wherein the binding protein comprises two or more zinc finger binding motifs.

Claim 25. The method according to claim 23, wherein the DNA binding protein is constructed by recombinant DNA technology, the method comprising the steps of:

- a) preparing a DNA coding sequence encoding two or more zinc finger binding motifs;
- b) inserting the DNA sequence into a suitable expression vector; and
- c) expressing the DNA sequence in a host organism in order to obtain the DNA binding protein.

Claim 26. The method according to claim 3 or 4 further comprising the steps of subjecting the DNA binding protein to one or more rounds of randomization and screening in order to improve the binding characteristics thereof.

Claim 28. The method of either of claims 3 or 4, further comprising detecting the DNA binding polypeptide binding to the target DNA sequence.

Claim 29. The method of either of claims 3 or 4, wherein the binding of the DNA binding polypeptide to the target DNA sequence regulates transcription of a gene.